Systemic and cerebral effects of prostacyclin-induced arterial hypotension in the dog

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Prostacyclin has strong vasodilating and antiplatelet properties. This study was performed to investigate its potential for producing profound intraoperative hypotension. Five dogs were anesthetized with morphine, nitrous oxide, and oxygen, paralyzed with pancuronium, and ventilated to a PaCO₂ of 40 torr. Mean arterial blood pressure (MABP) was lowered to 40 mm Hg with an intravenous infusion of prostacyclin in 0.05 M Tris buffer (average rate of infusion 3–1 μg/kg/min). Blood flow was determined using the radioactive microsphere technique. Measurements were made before and after 20, 40, and 60 minutes of hypotension; and after a 40-minute recovery period. Infusion of prostacyclin reduced MABP 63% while increasing heart rate 51%. Tachyarrhythmias occurred in all dogs, and cardiac index decreased 18%. Myocardial blood flow decreased an average of 29%, cerebral blood flow decreased 30%, cerebellar blood flow decreased 18%, and blood flow in the brain stem and spinal cord was unchanged. Cerebral metabolic rate of oxygen, determined by measuring the oxygen content of the sagittal sinus, was unchanged. Hypotension was easily induced and maintained using prostacyclin, without apparent tachyphylaxis. However, the cardiac changes caused by this drug are more severe than those accompanying hypotension induced by most other agents, and may represent a serious contraindication to its clinical use.

KEY WORDS: arterial hypotension, blood flow, prostacyclin

Prostacyclin is a prostaglandin produced by endothelium. Physiologically it appears to balance thromboxane by inhibiting thrombus formation and producing vasodilation. 14,16,24,34 It probably retards thrombus formation by preventing platelet adhesion and, especially, platelet aggregation. 17,30 In pharmacological doses, prostacyclin has been shown to be a vasodilator. 5,20,30,33 Its vasodilating properties and its apparent safety when given in pharmacological doses suggest that it could be a useful agent for inducing arterial hypotension during neurosurgical procedures. The purpose of this study was to document the cerebral and systemic circulatory effects of intravenous prostacyclin used to produce profound arterial hypotension.

Materials and Methods

Five mongrel dogs weighing approximately 15 kg each were used for this study. Anesthesia was induced with intravenous morphine, and nitrous oxide and oxygen (70:30). Muscular paralysis was achieved with pancuronium, 0.2 mg/kg initially and supplemented as needed. Ventilation was controlled with a pump respirator. The animals were hyperventilated and CO₂ was added to the inspired gas mixture to maintain an arterial pCO₂ of 40 torr. Temperature was maintained at 37°C with a warming blanket.

Blood flow was determined six times in each dog using the radioactive microsphere technique with 15 ± 5-μ spheres labeled with cerium-141, scandium-46, niobium-96, strontium-84, tin-113, and gadolinium-153. The microspheres were injected into the left ventricle utilizing a pigtail catheter inserted through the femoral artery and positioned manometrically. Blood reference samples were drawn from the right femoral and brachial arteries. At the completion of the experiment, the brain was removed and divided into cerebral hemisphere, gray and mixed gray and white samples, caudate nuclei, corpus callosum, brain stem, and cerebellum. In addition, samples of the cervical and spinal cord, temporalis and paraspinous muscles, left and right ventricles of the heart, liver, stomach, jejenum, and kidneys were removed for blood flow determinations. End-tidal CO₂ was monitored continuously. Central venous and pulmonary blood pressures were measured from a Swan-Ganz catheter inserted through a femoral vein. This
The thermodilution technique. Left ventricular pressure technique was also used to measure cardiac output with a chart recorder.

Parameters | Control | Hypotension | Recovery |
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PaO2 (mm Hg) | 153 ± 5 | 158 ± 2 | 164 ± 3 |
PaCO2 (mm Hg) | 39.4 ± 0.4 | 40.3 ± 0.1† | 40.2 ± 0.2 |
\(\text{pH} \) | 7.37 ± 0.03 | 7.31 ± 0.01† | 7.26 ± 0.02‡ |
\(\text{HCO}_3^− \) (mEq/liter) | 22 ± 2 | 20 ± 1 | 18 ± 1† |
\(\text{PAP} \) (mm Hg) | 38.0 ± 0.2 | 37.5 ± 0.1 | 36.8 ± 0.2† |
\(\text{SSP} \) (mm Hg) | 148 ± 3 | 148 ± 3 | 148 ± 3 |
\(\text{K}^+ \) (mg/dl) | 2.7 ± 0.1 | 3.8 ± 0.1§ |
\(\text{Na}^+ \) (mg/dl) | 98 ± 4 | 105 ± 1 |

* Values are expressed as mean ± standard error. The hypotension value is the average of the three hypotension determinations. The moderate metabolic acidosis which is not reversed during recovery.

Significance: † = p < 0.05; ‡ = p < 0.01; § = p < 0.001.

**TABLE 1**

Blood gases, temperature, hematocrit, and electrolytes in five dogs

**TABLE 2**

Cardiovascular parameters in five dogs

Results

Temperature, hematocrit, and electrolytes were not significantly changed throughout the course of the experiment, except for a slight rise in serum potassium. Arterial \(\text{pO}_2\) and \(\text{pCO}_2\) remained stable during the experiment. The \(\text{pH}\) and bicarbonate decreased, however, indicating the development of a metabolic acidosis during prostacyclin-induced hypotension. This acidosis had not improved at the recovery measurement (Table 1).

Prostacyclin infusion reduced MABP 63% compared with control levels. This was accompanied by a marked increase in the heart rate of 51%, with frequent tachyarrhythmias in all dogs. Both heart rate and blood pressure returned to control values after the recovery period. During hypotension, CI was reduced 18% and the stroke volume was reduced 50%. Both of these parameters remained depressed during the recovery phase. During hypotension, the peripheral vascular resistance decreased 53% while cardiac work was reduced 80%. Peripheral vascular resistance overshot control values during the recovery period by 50%, while cardiac work remained 30% below control values. There were no physiologically important changes in the central venous, pulmonary, or sagittal sinus pressures (Table 2 and Fig. 1).

Prostacyclin hypotension reduced blood flow to the left and right ventricle 32% and 25%, respectively, and during recovery these values remained 32% and 50% below control. In contrast, blood flow to the stomach and jejunum were both elevated during hypotension 23% and 79%, respectively. During the recovery phase,
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these flows were reduced 49% and 5% below their original level. Blood flow to the liver was reduced 77% during hypotension and showed little change during recovery. Kidney blood flow decreased 56% during prostacyclin infusion but recovered to 41% below control level during the recovery phase. Muscle blood flow decreased 40% to 50% during hypotension, but tended to recover after the infusion was discontinued. Total cerebral blood flow (CBF) decreased 28% during the hypotensive phase and showed no subsequent change during the recovery period (Table 3 and Fig. 2). Analysis of regional CBF demonstrated that total hemisphere, caudate nuclei, and cerebral cortex blood flows were reduced the most. Brain-stem blood flow was unaffected by prostacyclin hypotension. Recovery measurements showed that regional CBF was unchanged from the hypotensive values (Table 4 and Fig. 3).

The CMRO₂ was not statistically changed during hypotension or recovery, although there was a slight tendency for metabolism to decline over time. In contrast, cerebrovascular resistance was decreased 47% during the hypotensive period and overshoot the control value by 47% at the recovery phase (Table 5 and Fig. 4).

**Discussion**

Prostacyclin (PGI₂) is a highly active compound related to the prostaglandins. It is produced mainly in the endothelial and subendothelial layers of blood vessels by the conversion of prostaglandin H₂ (PGH₂) and via the lungs under some conditions, but the physiological importance of this mechanism is still unclear. The half-life of prostacyclin is 3 to 5 minutes, with no significant degradation occurring on passage through the lungs. There is some indication that its half-life in vitro may be somewhat longer when bound to albumin.

The action of prostacyclin includes vasodilatation and an inhibition of platelet aggregation and adhesion. The vasodilatation caused by prostacyclin varies, depending on the vascular bed involved and the dose of prostacyclin. In laboratory studies on cerebral vessels,
it has been shown that prostacyclin produces a biphasic response. Low doses cause vasodilatation, but superphysiological doses cause a vasoconstriction. The effect of prostacyclin on platelets is probably mediated through an increase in cyclic adenosine monophosphate (AMP), via a modulation of adenyl cyclase. It has been shown that prostacyclin prevents platelet aggregation at very low doses, but much higher doses are required to prevent platelet adhesion. Most of these effects are diametrically opposed to those caused by thromboxane (TXA2), which is also a product of PGH2. Thromboxane, however, is produced via thromboxane synthetase mainly in platelets. Thromboxane is known to cause vasoconstriction in most vascular beds and to cause platelet adhesion and aggregation. Abnormalities in the balance between prostacyclin and thromboxane have been implicated, along with other abnormalities in prostaglandin metabolism, in a variety of diseases including atherosclerosis, diabetes mellitus, cerebral vasospasm following subarachnoid hemorrhage, and cerebral edema from stroke or head injury.

Prostacyclin has been used experimentally for a wide variety of conditions including the treatment of coronary stenosis and impending occlusion, carotid stenosis, and cerebral vasospasm. It has been used clinically to treat severe atherosclerotic peripheral vascular disease, with some success. These studies have shown both an improvement in pain and healing and objective evidence of improvements in blood flow to the ischemic limbs. Prostacyclin has also been used for its antiplatelet aggregation action during extracorporeal bypass.

Fig. 3. Regional cerebral blood flows expressed as mean ± standard error for five dogs. The brain-stem blood flows remained stable throughout the experiment while other regions decreased in a fairly uniform fashion.

Fig. 4. Cerebral blood flow (CBF), metabolism, and cerebral vascular resistance (CVR) expressed as mean ± standard error. Cerebral metabolic rate of oxygen utilization (CMRO2) remained fairly stable while CBF and CVR fell during hypotension. Blood flow failed to return to control values during the recovery period. MAP = mean arterial pressure; SSP = sagittal sinus pressure.
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and thereby to reduce postsurgical bleeding due to loss of platelets.20

The prostacyclin doses used in this study were 100 to 1000 times those used in previous clinical studies. These doses, however, had no adverse effect on hematocrit, electrolytes, or blood gases, with the exception of the production of a mild metabolic acidosis. Since hypotension itself from any pharmacological manipulation is known to produce mild metabolic acidosis, this does not appear to be a specific problem associated with prostacyclin.

The effect of prostacyclin on the heart is variable, depending on the doses used. In this study, all dogs became profoundly tachycardic during the infusion of high doses of prostacyclin. The heart rate was frequently unstable and varied widely during the hypotensive period. Despite this tachycardia, CI was reduced only 18%. The profound peripheral dilatation reduced cardiac work 80% during the hypotensive period. The blood flow to the heart showed a moderate reduction during hypotension and during the recovery period. This may largely reflect a reduction in myocardial oxygen demand due to decreased cardiac work. There is some evidence that prostacyclin is a direct coronary vasodilator, and this may have moderated the reduction in flow. However, these changes in heart rate and CI are more severe than those associated with many other pharmacological agents for producing hypotension. High doses of prostacyclin might present a risk for use in patients with preexisting heart disease. The association of subarachnoid hemorrhage with myocardial damage would make those patients undergoing operation for intracranial aneurysm particularly susceptible to this complication. Blood flow to the stomach and jejunum were both elevated, and it has been noted in a variety of other studies that these vascular beds are dilated by lower doses of prostacyclin.20 The reduction in flow to the liver is most likely nonspecific, as it has been reported with a number of other hypotensive agents and is also seen simply as the result of prolonged anesthesia. The 56% reduction in renal blood flow is actually somewhat less profound than is seen with some other hypotensive agents.21 Prostacyclin in low doses has previously been reported to be a renal vasodilator.15,20 Blood flow to skeletal muscle sharply decreased with prostacyclin infusion, but then tended to recover promptly after discontinuation of the infusion.

Previous investigators have reported increases in CBF due to the intravenous or intra-arterial infusion of low doses of prostacyclin.18 The high dose of prostacyclin used in this study led to a decrease in total CBF and in all regional flows except that to the brain stem. The reductions in flow seen here are not significantly different from those seen in other hypotensive agents, and in fact most likely represent a change from the profound hypotension rather than a direct effect of the prostacyclin. The fact that total CBF decreased only 28% despite a 64% reduction in MAP indicates that functional autoregulation was still present. This is further dem-onstrated by the 47% reduction in cerebral vascular resistance despite a very minimal change in CMRO2.

Even with its favorable changes in blood flow during profound hypotension, however, the severe effects upon the heart caused by prostacyclin in high doses are a major drawback to its clinical use. It is unclear from this study whether these cardiac effects are direct or indirect, but it appears from the literature that there are direct and reflex cardiac responses to prostacyclin.3,7 Research in prostaglandin metabolism in recent years has led to many discoveries that could be of potential benefit in a variety of neurosurgical problems. Cerebral edema from a variety of causes, cerebral vasospasm secondary to subarachnoid hemorrhage, and embolic and thrombotic complications of atherosclerosis may all eventually be amenable to treatment by prostaglandins or prostaglandin modulators. At the present time, research is being conducted into specific thromboxane and prostacyclin synthetase modulators and into the development of a prostacyclin analog that does not cause severe cardiac disturbances.

References


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